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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/245,603	02/05/1999	DAVID T. CURIEL	678503-2012.2	5072

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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 11/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/245,603	CURIEL ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,9,11,16,22,23,30 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,9,11,16,22,23,30 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *10/18/05*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Final Rejection

Claims 1-4, 11, 16, 22-23, and 30-31 are pending.

Applicant's traversal, the cancellation of claims 26-29, the addition of claims 30 and 31 and the amendment to claims 1, 16 and 22 in paper filed on 8/26/05 is acknowledged and considered by the examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 9, 11, 16, 22, 23, and 30-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The limitation 'wherein the tripeptide is inserted into a homogeneous serotype fiber' in amended claims 1 and 16 and claims dependent therefrom is not supported by the instant specification. There appears to be a lack of written description of the limitation in the application as filed. See MPEP § 2163.06. Applicants assert that page 49, lines 4-10 provide support for the limitation. Page 49, lines 4-20 recites:

El-deleted Ad5 vectors, AdCMVLUC and MCMVLaCZ, which express firefly

respectively, were obtained from R. D. Gerard, the University of luciferase and bacterial p-galactosidase (1 8), Texas Southwestern Medical Center, Dallas, Texas.

To generate a gene encoding the Ad5 fiber knob domain with the Hl loop deleted, a PCR technique was employed. The following two pairs of primers were used:

F1: (5' TMGGATCCGGTGCCAUACAGTAGGMACMTM 3') (SEQ ID No . 1) ;

R1:(5' CATAGAGTATGCAGATATCGWAGTGWACAGGNAGNG 33 (SEQ ID No. 2);

F2: (5' GTMCACTMCGATATCTXATACTCTATGTCAUCATGG3') (SEQ ID No. 3); and

R2: (5' CCCAAXWACAAUGMMATMACACGTTGMACATAAC 33 (SEQ ID No. 4) were used to amplify portions of the fiber gene corresponding to positions 1159 to 1451 and 1642 to 1747, respectively.

Initially it is noted that literal support for the new terminology is not provided by the instant specification. Further, the figurative support is taken from the specification that provide specific working examples, not disclosure that would support the full breadth of the invention embracing an adenovirus comprising an RGD motif inserted into a homogeneous serotype fiber.

Page 49 only discloses the production of an Ad5 fiber knob domain with the HI loop domain deleted. Pages 52-53 disclose incorporating a RGD-4C peptide into the HI loop of a knob domain of an adenovirus via homologous recombination between two plasmids. In addition, a word search for the term "homogeneous" was performed on the

instant specification and the search did not result in a hit for the term. The definition of the term "homogeneous" in a dictionary (Merriam Webster's Collegiate Dictionary, 10th edition, Merriam-Webster, Incorporated, page 554, 2001) used by the skilled artisan is "as the same or a similar kind or nature." The limitation reads on an adenovirus having a RGD motif inserted into HI domain of the adenovirus fiber protein, wherein the fiber protein can be the same or a similar kind or nature. Thus, the limitation reads on an adenovirus fiber protein or a chimeric adenovirus fiber protein because both fiber proteins are similar in nature.

Thus, nothing in the specification would lead one to the particular limitations set forth in the amended claims 1 and 16 and claims dependent therefrom set forth in the instant application.

Applicant's arguments, see pages 6-7, filed 8/26/05, with respect to 112 new matter rejection have been fully considered and are persuasive. The rejection of claims 1-4, 9, 11, 16, 22, 23, and 26-29 has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of the amendment to claims 1 and 16.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The instant claims read on a recombinant adenovirus (replication competent or replication defective) comprising a modified fiber comprising a tripeptide RGD in any part of the HI loop domain of the fiber knob and methods of using the recombinant adenovirus.

In addition, the limitation "that mediates enhanced gene transfer to primary tumor cells" in the instant claims does not have patentable weight over the prior art because the limitation does not disclosed a structural feature of the adenovirus that would distinguished from the prior art. See MPEP 2111.02.

Claims 1-4, 9, 11, 16, 22, 23, and 30-31 are rejected under 35 U.S.C. 102(e) as being anticipated by Wickham et al. (US 5,846,782). The previous rejection is maintained for the reasons of record advanced on pages 3-5 of the Office action mailed on 2/26/03. Furthermore, Wickham teaches the adenovirus can have a fiber from Ad5 (columns 5 and 13).

Applicant's arguments filed 8/26/05 have been fully considered but they are not persuasive.

In response to applicant's argument that '782 relates to the use of an adenovirus 5 serotype vector wherein ligands are inserted into the HI loop of an Ad2 serotype vector,

thereby providing an Ad5/Ad2 fiber chimera and the '782 patent does not teach or suggest the insertion of any ligand into a homogeneous serotype fiber. The argument is not found persuasive because Wickham teaches using an adenovirus encoding a tripeptide (RGD) in the HI loop domain of the fiber knob. The adenovirus fiber can be from any adenovirus (column 13). See Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). See also Celeritas Technologies Ltd. v. Rockwell International Corp., 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir.1998). In addition, the argument is not found persuasive because it appears applicant is arguing that by amending the claims with the phrase "homogeneous serotype fiber" the claimed invention is not taught by Wickham because the preferred embodiment of Wickham is directed to making chimeric adenovirus fiber protein comprising Ad5/Ad2. However, the instant specification does not define the term "homogeneous" and upon consideration of the definition of the term "homogeneous" in a dictionary (Merriam Webster's Collegiate Dictionary, 10th edition, Merriam-Webster, Incorporated, page 554, 2001) used by the skilled artisan, '782 still reads on the claimed invention. Homogeneous is defined as "as the same or a similar kind or nature." Thus, an Ad5/Ad2 fiber protein is similar to either an Ad2 fiber protein or an Ad5 fiber protein comprising a RGD motif in the HI loop because all of them are adenovirus fiber proteins.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 9, 11, 16, 22, 23, and 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wickham et al. 1 (WO 96/26281, cited on a PTO-1449) taken with Wickham et al. 2 (US 5,846,782).

Wickham et al. 1 teaches incorporating a non-native binding domain within an exposed loop of a mutant adenovirus to create a fiber chimera and producing recombinant adenovirus comprising the fiber chimera (pages 9 and 10). Wickham et al. 1 teaches the limitation in instant claims 2 and 4 because there is not additional structure that

distinguished that adenovirus from the adenovirus in claim 1 of the instant application (pages 9 and 16). However, Wickham et al. 1 does not specifically teach that the exposed loop of the adenovirus is the HI loop of the fiber knob.

However, at the time the invention was made, Wickham et al. 2 teaches producing adenoviruses comprising a modified fiber protein containing an RGD motif (columns 9 and 20-21). Wickham et al.. 2 teach that the exposed loop is preferably the HI loop of the fiber knob (columns 20-21). Wickham 2 teaches the adenovirus can have a fiber from Ad5 (column 5). Wickham teaches the adenoviral vector encodes a therapeutic gene, thymidine kinase (columns 13-14). Wickham teaches introducing the adenoviral vector into cancer cells (column 17). Accordingly, in view of the prior art represented by Wickham et al. 1 and 2, one of ordinary skill in the art would have had sufficient motivation to produce recombinant adenoviruses containing a RGD motif in the HI loop domain of the fiber knob with a reasonable expectation of success.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wickham et al. 1 taken with Wickham et al. 2, namely to insert an RGD motif into the HI loop domain of the fiber knob of a recombinant adenovirus. One of ordinary skill in the art would have been motivated to combine the teaching because Wickham et al. 2 teaches that the adenovirus is more efficient for entry into cells compared to an adenovirus with a wild-type fiber protein.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wickham et al. 1 taken with Wickham et al. 2, namely to use the recombinant adenovirus to kill tumor

cells. One of ordinary skill in the art would have been motivated to combine the teaching because Wickham et al. 2 teaches that the adenovirus is more efficient for entry into cells compared to an adenovirus with a wild-type fiber protein.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 8/26/05 have been fully considered but they are not persuasive.

In response to applicant's argument that '281 publication does not teach or suggest inserting any ligand, let alone an RGD peptide, into a homogeneous serotype fiber. In fact, Examples 3 and 5 of the '281 publication relate to inserting an RGD into a chimeric, i.e., heterogeneous, serotype fibers.

The argument is not found persuasive because Wickham1 taken with Wickham2 teaches using an adenovirus encoding a tripeptide (RGD) in the HI loop domain of the fiber knob. In addition, it appears that applicant is arguing that by amending the claims with the phrase "homogeneous serotype fiber" the claimed invention is not taught by Wickham because the preferred embodiment of Wickham is directed to making chimeric adenovirus fiber protein comprising Ad5/Ad2. However, the instant specification does not define the term "homogeneous" and upon consideration of the definition of the term "homogeneous" in a dictionary (Merriam Webster's Collegiate Dictionary, 10th edition, Merriam-Webster, Incorporated, page 554, 2001) used by the skilled artisan, '281 taken with '782 still is obvious over the claimed invention. Homogeneous is defined as "as the same or a similar kind or nature." Thus, an Ad5/Ad2 fiber protein is similar to either an

Ad2 fiber protein or an Ad5 fiber protein comprising a RGD motif in the HI loop because the fiber proteins are adenovirus fiber proteins.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 4, 9, 11, are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, and 12 of U.S. Patent No. 6,824,771. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims from '771 embraced a recombinant adenovirus having a modified fiber protein containing RGD in the HI loop domain of the fiber knob. The instant claims are directed to a recombinant adenovirus comprising a modified fiber gene, wherein the modified fiber gene comprises a cDNA encoding a tripeptide having the sequence RGD in the HI loop domain of the fiber knob and using the adenovirus in a method of killing tumor cells.

The claims from '771 are directed to using a conditionally replicative adenovirus in a method treating tumors in a subject, wherein the fiber gene encodes a cDNA

encoding a tripeptide having the RGD motif in the HI loop domain of the fiber knob. The instant claims embrace a replication competent or replication defective adenovirus comprising a RGD motif in the HI loop domain of the fiber knob. However, the claims from '771 do not specifically recite the limitation in instant claims 4, 9, and 11. In addition, the limitation in instant claim 4 would be an obvious variant of the claims 1 and 2 from '771 because the fiber knob of the adenovirus would have to be able trimerize and retain its biosynthesis profile for the adenovirus to infect tumor cells. The limitation in instant claim 9 and instant claim 11 would be obvious variants of claims 1 and 12 from '771 in light of the specification of '771 teaching using a nucleotide sequence encoding a thymidine kinase as the exogenous nucleotide sequence in claim 12 of '771. See Figure 2 of '771. Therefore, the claims of the instant application and US patent '771 are obvious variants of one another.

Applicant's arguments filed 8/26/05 have been fully considered but they are not persuasive. In response to applicant's argument that upon agreement as to allowable subject matter, it is believed that there is still a double patenting issue, a terminal disclaimer as to the '771 patent will be filed for the purpose of expediting prosecution, the argument is not found persuasive because the claims still overlap with claims from '771 and a terminal disclaimer is required to overcome the rejection.

Response to Arguments

Applicant's arguments, see page 7, filed 8/26/05, with respect to 112 second paragraph rejection have been fully considered and are persuasive. The rejection of claims 16, 22, 23, 27, and 29 has been withdrawn.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, acting SPE – Art Unit 1635, can be reached at (571) 272-0811.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman
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